ENDOTHELIAL HETEROGENEITY AND ORGAN-SPECIFICITY: INTERPLAY BETWEEN MICROENVIRONMENTAL CLUES AND HEMODYNAMIC MILIEU

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Recent studies have demonstrated a remarkable heterogeneity and organ-specificity of vascular endothelial cells (ECs). We and other have previously shown in vitro that coculture of endocrine parenchymal cells and microvascular ECs from the same organ results in bidirectional signals, which might be consequential for the organ-specific differentiation of both cell types. These juxtacrine signals include cell-cell contacts, humoral factors and cues in the extracellular matrix. Ultrastructural studies in the developing rat adrenal medulla imply that heterotypic cell-cell contacts between immature chromaffin cells and EC precursors precede the expression of fenestration of organotypic capillaries as well as the functional maturation of the organ. Furthermore, differential lectin staining in vivo reveals a delicate fine tuning of organspecific post translational modifications (e.g. glycosylation patterns) of both ECs and the subendothelial basement membrane. We hypothesize that organ-specificity is the cumulative expression of specific post-translational modifications and/or the expression of unique genes under the control of organ-specific promotor/regulatory elements.

It is increasingly being appreciated the ECs do not merely form the ubiquitous, uniform lining of the vessel walls, but that they display a plethora of phenotypic and functional disparities, depending on their location within the vascular tree. Some of these differences are maintained throughout many passages in culture, some others are rapidly lost suggesting an interplay between genetic and epigenetic modulations of the EC phenotype. We hypothesize that the hemodynamic environment is one of the major epigenetic cues, which determine distinct EC functions and phenotypes. To test this hypothesis, we are culturing ECs under dynamic regimens, which include pulsatile, non-uniform flow fields, cyclic strain and elevated mean pressure. In these settings, we observed differential activation of thrombomodulatory (e.g. tissue factor, tPA, PAI-1) and vasomodulatory (e.g. ACE, ET) responses of various EC types. To understand the cellular mechanisms of hemodynamic regulation we and others are exploring distinct signal transduction pathways. For example, close scrutiny of the adenylate cyclase pathway reveals significant differences between venous, arterial and microvascular ECs, both under basal and stimulated (specific agonists and cyclic-strain) conditions. Synergism between both types of activators suggests that EC perceive and respond to mechanical signals by utilizing and modulating common pathways of intracellular signal transduction. Future research will reveal whether there are specialized mechanoreceptors and/or mechano-responsive elements which govern endothelial cell heterogeneity.

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